Amendments to the Claims:

Amendments to and cancellations of claims are made without prejudice or disclaimer. This listing of claims replaces all prior versions and listings of claims in the application:

Listing of Claims:

1. (currently amended) A method executed by a computer under the control of a program, said computer including a memory for storing said program, said method comprising the steps of:

providing an ensemble of related backbone structures;

applying a protein design algorithm to generate a protein sequence or set of protein sequences;

sampling and evaluating fitness of one or more amino acids ~~or rotamers within the context of said protein sequence or set of protein sequences and~~ at positions in at least one backbone structure; and

generating a probability matrix for said amino acids ~~or rotamers~~ that represent a viable sequence space for said ensemble of backbone structures.

2. (original) A method according to claim 1 further comprising the step of: generating a single protein sequence from said probability matrix.

3. (currently amended) A method according to claim 1 further comprising the step of: ~~generating~~ producing a combinatorial library of proteins from said probability matrix.

4. (original) A method according to claim 1 wherein said steps are repeated more than once to generate said probability matrix

5. (original) A method according to claim 1 wherein said protein design algorithm comprises an optimization procedure selected from the group of: dead end elimination algorithm; genetic algorithm; Monte Carlo algorithm; and self consistent mean field theory algorithm or combinations thereof.

6. (previously presented) A method according to claim 1 wherein at least one backbone structure of the ensemble is derived from the structure of a natural protein.

7. (previously presented) A method according to claim 1 wherein at least one backbone structure of the ensemble is generated by comparative modeling.

8. (currently amended) A computer-executable method comprising:

receiving at least one protein backbone structure;

generating at least two probability matrices that each represent the viable sequence space for the protein backbone subject to a constraint; and

combining information from said probability matrices to satisfy at least two constraints on sequence space.

9. (canceled)

10. (canceled)

11. (canceled)

12. (previously presented) A method according to claim 8 wherein said steps are repeated more than once to generate said probability matrix.

13. (previously presented) A method according to claim 8 wherein said generating step comprises a protein design algorithm that comprises an optimization procedure selected from the group of: dead end elimination algorithm; genetic algorithm; Monte Carlo algorithm; and self consistent mean field theory algorithm or combinations thereof.

14. (previously presented) A method according to claim 1 wherein said ensemble of related backbone structures comprises backbone structures of a family of natural proteins.

15. (withdrawn) A method according to claim 1 wherein said ensemble of related backbone structures is derived from an NMR structure.

16. (previously presented) A method according to claim 1 wherein said ensemble of related protein backbone structures is generated by a Monte Carlo simulation.

17. (withdrawn) A method according to claim 1 wherein said ensemble of related protein backbone structures is generated by a molecular dynamics simulation.

18. (previously presented) A method according to claim 1 wherein the information from at least two probability matrices is combined to satisfy at least two constraints on sequence space.

19. (currently amended) A method comprising the computer-executable steps of:

receiving at least one protein sequence and structure; and

generating a probability matrix for amino acids that represent the viable sequence space for said protein backbone by evaluating fitness of one or more amino acids ~~within the context of~~ at positions in said protein sequence and structure.

20. (previously presented) A method according to claim 19 wherein said protein sequence and structure correspond to that of a natural protein.

21. (previously presented) A method according to claim 19 wherein an ensemble of related protein structures is generated from said received protein sequence and structure.

22. (original) A method according to claim 21 wherein said ensemble of proteins is generated by a Monte Carlo simulation.

23. (withdrawn) A method according to claim 21 wherein said ensemble of proteins is generated by a molecular dynamics simulation.

24. (original) A method according to claim 19 wherein said steps are repeated more than once to generate said probability matrix.

25. (currently amended) A method according to claim 19 further comprising the step of: producing a protein that comprises a single protein sequence from said probability matrix.

26. (previously presented) A method according to claim 19 further comprising the step of: producing a library of proteins from said probability matrix.

27. (original) A method according to claim 19 wherein said protein sequence and structure is generated by comparative modeling.

28. (original) A method according to claim 19 wherein said protein sequence and structure is taken from a natural protein.

29. (original) A method according to claim 19 wherein the information from at least two probability matrices is combined to satisfy at least two constraints on sequence space.

30. (withdrawn) A method for optimizing simulation or scoring function parameters that utilizes comparisons between designed sequences and natural sequences, comprising the steps of: designing a protein sequence; comparing said designed protein sequence to natural protein statistics; modifying said simulation or scoring function parameters consistent with said comparison.

31. (withdrawn) A method according to claim 30 wherein said steps are repeated at least once.

32. (withdrawn) A method according to claim 30 wherein said natural protein statistics are in the form of a position specific scoring matrix.

33. (withdrawn) A method according to claim 30 wherein said natural protein statistics are in the form of amino acid composition.

34. (original) A method for optimizing simulation or scoring function parameters that utilizes comparisons between designed sequences and natural sequences, comprising the steps of: calculating an amino acid probability matrix; comparing said matrix to natural protein statistics; modifying simulation or scoring function parameters consistent with said comparison.

35. (withdrawn) A method according to claim 34 wherein the sequence of steps is repeated at least once.

36. (withdrawn) A method according to claim 34 wherein said natural sequence statistics are in the form of a position specific scoring matrix.

37. (withdrawn) A method according to claim 34 wherein said natural sequence statistics are in the form of amino acid composition.

38. (previously presented) A method according claim 25 wherein the amino acid sequence of the single protein sequence is selected by identifying the amino acid with the lowest free energy at each position.

39. (currently amended) A method according claim 26 ~~wherein the library is designed by a procedure~~ further comprising selecting an upper limit on free energy, allowing amino acid variations among amino acids that are below the upper free energy limit, to thereby identify a library of protein sequences from said probability matrix.

40. (currently amended) A method according claim 26 ~~wherein the library is designed by a procedure~~ further comprising incorporating amino acids at incrementally lower probabilities until a desired complexity is achieved, thereby identifying a library of protein sequences from said probability matrix.

41. (previously presented) A method according to claim 8 wherein the at least two constraints comprise a first constraint corresponding to a first structural form and second constraint corresponding to a second structural form that is distinct from the first structural form.

42. (previously presented) A method according to claim 8 wherein a first and second probability matrix are combined by adding or subtracting free energies values from said probability matrices.

43. (previously presented) A method according to claim 8 wherein the combining process is iterated.

44. (currently amended) The method of claim 1 wherein the sampling an amino acid position comprises freezing side chain identities and rotamers at ~~all other~~ positions in the protein other than the sampled amino acid position.

45. (previously presented) The method of claim 1 wherein the probability matrix is expressed as a set of partition functions.

46. (previously presented) The method of claim 1 wherein the probability matrix is expressed as a free energy value.

47. (previously presented) The method of claim 1 wherein the probability matrix comprises information for all twenty amino acids.

48. (previously presented) The method of claim 3 further comprising screening or selecting one or more proteins from the library.

49. (previously presented) The method of claim 4 wherein, in a subsequent cycle, the protein design algorithm uses the probability matrix from a previous cycle.

50. (currently amended) The method of claim 48 wherein the screening or selecting comprises identifying a protein with enhanced activity, improved thermodynamic stability, or altered specificity, relative to an initial protein whose backbone structure is one of the backbone structures of the ensemble.

51. (currently amended) A method comprising:

generating a first probability matrix for amino acids at positions in a protein sequence by evaluating fitness of rotamers of a plurality of amino acids ~~within the context of the protein sequence and~~ for a structure or structures subject to a first constraint on sequence space;

generating a second probability matrix for amino acids at positions in the protein sequence by evaluating fitness of rotamers of a plurality of amino acids ~~within the context of the protein sequence and~~ for a structure or structures subject to a second constraint on sequence space; and

combining information from at least the first and second probability matrices to satisfy at least the first and second constraints on sequence space, to provide information about a sequence space compatible with the first and second constraints.

52. (previously presented) The method of claim 51 wherein the first and second constraints correspond to two distinct structural forms.

53. (previously presented) The method of claim 51 wherein the information is combined by adding or subtracting free energies.

54. (previously presented) The method of claim 51 wherein the information is combined iteratively.

55. (previously presented) The method of claim 54 wherein the information is combined iteratively until convergence is attained.

56. (previously presented) The method of claim 51 further comprising, prior to generating the first and second probability matrix, applying a protein design algorithm to generate a protein sequence for a protein backbone structure.

57. (withdrawn) A method comprising:

for each of an ensemble of related protein structures, identifying a set of side chain identities and rotamer orientations suitable for the respective protein structure;

updating a matrix representing fitness of amino acid rotamers at positions in the protein by sampling rotamer fitness in the context of each identified set of side chain identities and rotamer orientations; and

repeating the step of identifying at least once, wherein a subsequent step of identifying uses the updated matrix to identify set of side chain identities and rotamer orientations suitable for the respective protein structure.

58. (withdrawn) An article of computer-accessible memory that has instructions for directing a computer to execute a method comprising:

for each structure of an ensemble of related protein structures, identifying a set of side chain identities and rotamer orientations suitable for the respective protein structure;

updating a matrix representing fitness of amino acid rotamers at positions in the protein structures by sampling rotamer fitness in the context of each identified set of side chain identities and rotamer orientations; and

repeating the step of identifying at least once, wherein a subsequent step of identifying uses the updated matrix to identify set of side chain identities and rotamer orientations suitable for the respective protein structure.

59. (withdrawn) A computing apparatus comprising: a central processor, a memory, and an input/output bus,

the memory being configured to store a matrix representing fitness of amino acid rotamers at a plurality of positions in a model of a protein,

the processor being configured to execute a method comprising:

for each structure of an ensemble of related protein structures, identifying a set of side chain identities and rotamer orientations suitable for the respective protein structure;

updating the matrix stored in the memory by sampling rotamer fitness in the context of each identified set of side chain identities and rotamer orientations; and

repeating the step of identifying at least once, wherein a subsequent step of identifying uses the updated matrix in the memory to identify set of side chain identities and rotamer orientations suitable for the respective protein structure.

60. (previously presented) A method of providing a protein, the method comprising:

performing the method of claim 1; and

producing at least one protein comprising a sequence based on said probability matrix.

61. (previously presented) A method of providing a protein library, the method comprising:

performing the method of claim 1; and

producing a library of proteins that include proteins that each comprise a sequence based on said probability matrix.

62. (withdrawn) A library of proteins comprising a plurality of proteins designed by the method of claim 3.

63. (withdrawn) A protein comprising an amino acid sequence designed by the method of claim 2.

64. (previously presented) A method executed by a computer under the control of a program, said computer including a memory for storing the program, the method comprising:

providing an ensemble of related backbone structures; and

applying a design procedure to generate a protein sequence or set of protein sequences.

65. (previously presented) A method executed by a computer under the control of a program, said computer including a memory for storing the program, the method comprising:

providing an ensemble of related backbone structures; and

generating a matrix of amino acid probabilities that represents a viable sequence space for said ensemble of backbone structures.

66. (withdrawn) A method comprising the computer-executable steps of:

receiving at least one complete protein sequence and structure;

sampling and evaluating one or more amino acids and rotamers within the context of said complete protein sequence and structure; and

generating a probability matrix for said amino acids and rotamers that represent the viable sequence space for said protein structure.

67. (new) The method of claim 1 wherein the step of sampling and evaluating fitness of one or more amino acids comprises sampling and evaluating fitness of different rotamers of the one or more amino acids at position in at least one backbone structure.

68. (new) The method of claim 3 further comprising producing a protein that comprises the single protein sequence.